Canine hypothyroidism: diagnosis and treatment

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Primary canine hypothyroidism is mainly caused by immune-mediated destruction or idiopathic atrophy of the thyroid gland. In the first case, the thyroid gland becomes progressively infiltrated with lymphocytes and macrophages (lymphocytic thyroiditis). This leads to a gradual destruction of thyroid tissue and inevitably to reduced thyroid hormone production. Idiopathic thyroid atrophy or degeneration is characterized by a loss of functional thyroid parenchyma, which is replaced by adipose or fibrous connective tissue. Its cause is not yet clear; however it is likely that at least a proportion of these cases represent an end-stage form of lymphocytic thyroiditis.

Physiological background

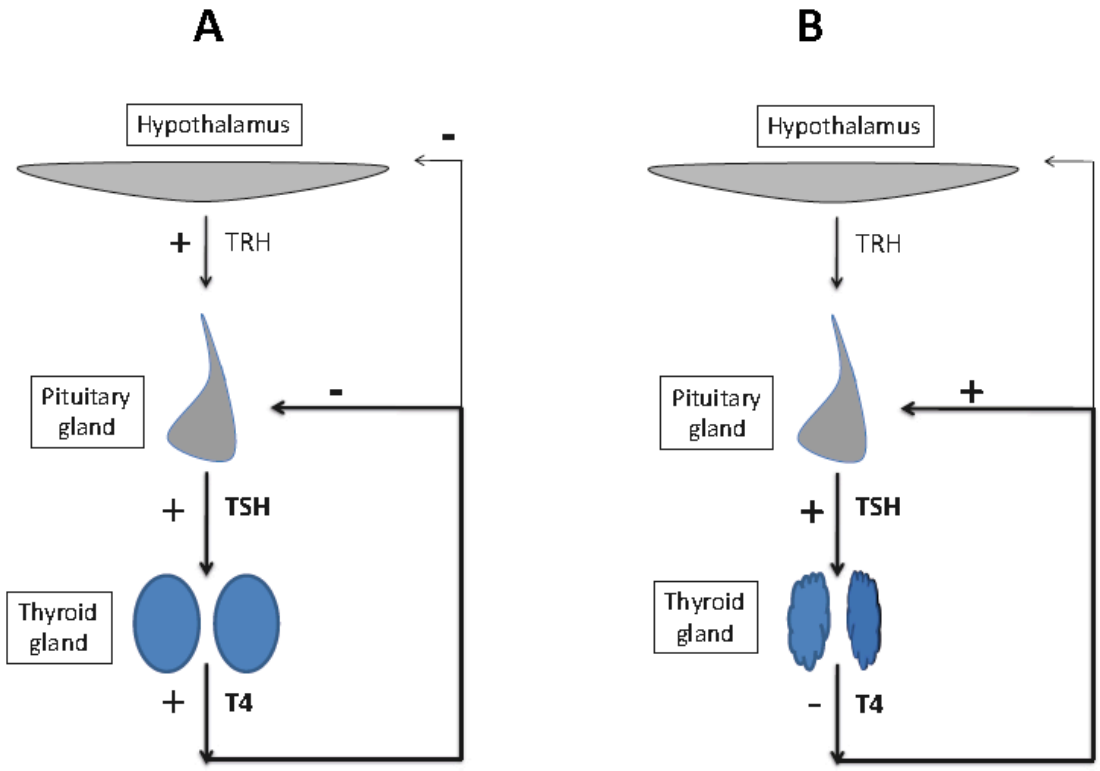

Figure 1: Regulation of thyroid hormone secretion: The hypothalamic-pituitary-thyroid axis. Thyroid hormones (e.g. T4) exert negative feedback at the pituitary and hypothalamic levels. Thyroid stimulating hormone (TSH) causes the synthesis and release of thyroid hormones, which in turn lead to a decrease in TSH (Fig. A). In thyroid gland failure (hypothyroidism), the decreased concentration of thyroid hormones leads to an increased synthesis and secretion of TSH (Fig. B).

Clinical symptoms and clinicopathological findings

The progression of the disease is slow, and clinical signs are not expected to occur unless at least 75% of the thyroid is affected. As thyroid hormones have a wide variety of physiological effects on many organ systems, clinical signs of hormone deficiency are broad and unspecific. Often they are attributable to a decreased metabolic rate such as lethargy, unwillingness to walk, exercise intolerance and weight gain despite normal appetite. Other common findings are dermatological abnormalities, including seborrhea, hair thinning and alopecia, particularly affecting the flanks and tail, skin hyperpigmentation and superficial pyoderma. Less common signs include neuromuscular, gastrointestinal, cardiovascular, ocular and reproductive

abnormalities. Most important routine clinicopathologic changes include a mild to moderate non-regenerative anemia, hypercholesterolemia and hypertriglyceridemia.

Specific tests of thyroid gland function

Clinical symptoms as well as changes in complete blood count (CBC) and serum blood chemistry often lead to a first suspicion. However, confirmation of the diagnosis necessitates specific testing of the thyroid function and confirmation of the diagnosis can sometimes be challenging.

Total T4 (thyroxine) concentration

Determination of T4 is a useful screening test and is particularly helpful in ruling out hypothyroidism as approximately 98% of the hypothyroid dogs have low T4 concentrations. It is relatively stable even at room-temperature and can be sent to outside laboratories. However, although low serum T4 concentrations are intuitively suggestive of hypothyroidism, it must be considered that low T4 levels are frequently encountered in euthyroid dogs with various non-thyroidal diseases (euthyroid sick syndrome/nonthyroidal illness syndrome) and dogs receiving certain medication (Table 1). Moreover, fluctuations in T4 even below the reference range also occur in healthy dogs. Also, one must remember that certain breeds of dogs, e.g. sighthounds, Alaskan sled dogs, Dogue de Bordeaux and Giant Schnauzer, have lower T4 concentrations compared to other breeds. Therefore, a T4 concentration below the reference interval cannot confirm hypothyroidism, however, a normal serum T4 concentration can confirm normal thyroid gland function unless serum T4 autoantibodies are present and interfering with the assay (see below).

Table 1: Influence of certain drugs on thyroid hormone parameters

Drug	**T4**	**fT4**	**cTSH**
Glucocorticoids	↓	↓	= oder ↓
Phenobarbital	= oder ↓	= oder ↓	= oder ↑
Potassium bromide	=	=	=
Imepitoin	=	=	=
Clomipramine	↓	↓	=
Sulfonamides	↓	↓	↑
Carprofen	↓=	= oder ↓	↓
Ketoprofen	↓	=	=
Deracoxib	=	=	=

Serum free T4 concentration

The metabolically active fraction of T4, free T4 (fT4), is widely acknowledged to more closely reflect the thyroid status than T4. Determination of fT4 by equilibrium dialyses has been suggested as an alternative, noninvasive means and by some authors is considered more sensitive and specific than the determination of T4. However, two major considerations have to be taken into account. Firstly, the equilibrium dialyses method for determination of fT4 is an expensive analysis that is not offered by many laboratories (e.g. in Europe it is offered only in Cambridge, UK) and samples have to be sent on dry ice. Secondly, some dogs without hypothyroidism, especially those with euthyroid sick syndrome or dermatopathies, or those receiving glucocorticoids, may also have decreased fT4 concentrations. Therefore the determination of fT4, particularly in dogs from German-speaking countries, is not a viable option in confirming the diagnosis. However, fT4 should be determined if Anti-T4 autoantibodies (T4AA) are suspected (see below).

Canine/endogenoues cTSH (thyrotropin)

Endogenous thyroid stimulating hormone (TSH) levels in the circulation are expected to be increased during states of low T4 (Figure 1). In contrast to human medicine, using the currently

available cTSH assays, normal cTSH concentrations cannot exclude the presence of hypothyroidism in dogs. Several reasons have been discussed to explain the low sensitivity of only 63-87%: secondary hypothyroidism (pituitary problem) more common than previously thought, physiological variations, exhaustion of the pituitary gland (TSH-producing cells) after longer-standing hypothyroid condition, existence of different TSH isoforms that are not recognized by current available cTSH assays.
Specificity of an increased cTSH is rather high with values up to 98%, however, few exception can lead to falsely increased values: treatment with sulfonamides, recovery phase of a non-thyroidal disease, after cessation of thyroxine trial therapy, during trilostane treatment, in dogs with primary hypoadrenocorticism before glucocorticoid treatment.

Thyroglobulin Autoantibodies (TgAA), T4 and T3 Autoantibodies (T4AA, T3AA)
The presence of thyroiditis in dogs can be detected by the measurement of antibodies to thyroid components in the serum, usually antithyroglobulin antibodies (TgAAs). In contrast to humans with thyroiditis, in which antibodies are most commonly directed against thyroperoxidase (TPO), anti-TPO-antibodies are of minor importance in dogs. In a large number of dogs in the United States, the distribution of the two forms (lymphocytic thyroiditis and atrophy) was estimated at approximately 1:1. However, there seems to be considerable variation among different breeds and a tendency toward lymphocytic thyroiditis at an earlier age. The absence of inflammation is likely to result in the disappearance of antibodies from the circulation over time. What contribution this end-stage of thyroiditis makes to the 50% of canine hypothyroidism that is antibody-negative (idiopathic) has not yet been defined. Although a positive TgAA result is strong evidence of thyroid disease, its measurement cannot be used to predict whether clinically relevant destruction will occur. It has been suggested that of TgAA positive dogs, approximately 15% become antibody negative over time and remain euthyroid thereafter; another 20% develop thyroid hormone abnormalities suggestive of declining thyroid function and about 5% become overtly hypothyroid within 12-18 months. Whether these results also hold true for the general population remains to be determined. Important to remember for the clinician is that determination of TgAA is not helpful in confirming the diagnosis as detection of TgAAs provides no information on thyroid function.
Part of TgAAs also reacts against T3 and T4 and these antibodies may interfere with hormone assays leading to a spurious increase (most common) or decrease in the measured hormone concentration. T4AA could increase a low T4 concentration into the normal or high range and result in a false diagnosis of euthyroidism in a hypothyroid dog, which has to be taken into consideration in interpreting testresults. If suspicion of hypothyroidism is high but the T4 concentration is normal or even increased, T4AA should be determined in addition to the determination of fT4. Determination of fT4 using equilibrium dialysis is not influenced by the presence of T4AA.

TSH-Stimulation test
The TSH stimulation test has long been considered an accurate test, and some authors still recognize it as the “gold standard” for confirming the diagnosis of canine hypothyroidism. Determination of circulating T4 before and 6 hours after the administration of exogenous TSH (recombinant human TSH, Thyrogen®) provides an assessment of the functional reserve capacity of the thyroid gland, with minimal to no stimulation expected in hypothyroidism. In euthyroid dogs, post-TSH T4 concentrations are expected to be higher than 30 nmol/L, depending on the T4 assay that is used. An increase of less than 1.5 times basal T4 or post-TSH-T4 concentration lower than 20 nmol/L are consistent with hypothyroidism. The test seems to be less influenced by nonthyroidal illness and by medications known to affect thyroid function, however, results in the “grey-zone” are also possible. If testing cannot be delayed, the discriminatory power of the TSH stimulation test to differentiate between euthyroid-sick and primary hypothyroidism, can be improved if a dose of 150ug recombinant TSH is used, independent of the dog`s body-weight. The costs of the product are rather high, however, reconstituted rhTSH can be stored at 4°C for 4 weeks or −20°C for up to 12 weeks. This allows multiuse from one vial making the test somehow affordable, although it remains expensive compared to other tests.

Table 2: Overview of sensitivity, specificity and accuracy of specific parameters in the diagnosis of canine hypothyroidism (summarized from (Dixon & Mooney, 1999; Kantrowitz, Peterson et al., 2001; Boretti & Reusch, 2004; Ferguson, 2007; Scott-Moncrieff, 2015))

Parameter	**Sensitivity**	**Specificity**	**Accuracy**
Low T4	89 %	75-82 %	85 %
Low fT4 (equ. Dialyse)	80-98 %	93-94 %	95 %
High cTSH	60-87 %	82-100 %	84 %
Low T4 and high cTSH	67-87 %	92-100 %	82 %
Low fT4 and high cTSH	74-80 %	97 -98 %	86 %

Diagnostic imaging

Ultrasound (US)

Ultrasound of the thyroid glands can be used as additional test to support the diagnosis. In hypothyroid dogs they are expected to have a smaller volume, irregular margins and a hypoechegenic parenchyma compared to surrounding muscles. A high-frequency ultrasound "head" with at least 10MHz operated by an experienced ultrasonographer is a prerequisite. However, one should be aware that US cannot replace biochemical examination and using this modality will not lead to a final diagnosis in all cases.

Scintigraphy

By some authors, scintigraphic examination of the thyroid gland using technetium-99 (pertechnetate) has been suggested as the most accurate technique for distinguishing dogs with primary hypothyroidism from those with non-thyroidal illness. However, results from recent studies have shown that there are factors, especially glucocorticoids that can influence and decrease uptake, leading to equivocal results. Moreover, due to technical enormous requirements, this modality cannot be used in daily life of a practitioner.

Treatment and monitoring

Synthetic thyroid hormone replacement in the form of oral sodium levothyroxine (synthetic T4) is the treatment of choice. Recommendation for initiation of therapy is a starting dose of 20 µg/kg BW twice daily, lower doses may be sufficient in some dogs and some authors also recommend once daily dosing. However, twice-daily dosing is associated with less fluctuation in T4 and lower peak concentrations. Therefore, once daily should only be initiated only if clinical signs are well controlled. A liquid formulation is also available, which (according to the manufacturer) can be administered once daily at a dosage of 20 µg/kg BW once daily, although in selected dogs a change to twice daily can be necessary to control clinical symptoms.

In dogs with concurrent cardiovascular disease or hypoadrenocorticism, treatment should be instituted at 25% of the standard dose, with an increase of 25% every 2 weeks based on clinical response and post-pill testing.

Gastrointestinal absorption of T4 is very low and its bioavailability is further decreased when administered with food. Pilling on an empty stomach is not a prerequisite for a therapeutic success, however, owners should be instructed to standardize time between feeding and oral dosing and it should be the same time interval on the day of T4 monitoring as always.

Serum T4 should be determined at peak T4 concentration, which occurs about 4-6 hours after administration. At that time point T4 should be in the high normal or slightly above the reference interval. Serum TSH concentrations should be within the reference interval; unfortunately, due to the low analytic sensitivity of the current cTSH assays, they do not allow identification of oversupplementation.

A positive response to therapy should be observed within the first 4-6 weeks after starting treatment. Improvements in physical activity and in mentation can occur after 1 week, however other signs, especially dermatological signs may take several weeks to months to improve and resolve.
Reasons for treatment failures or incomplete response may be the following: Incorrect diagnosis, concurrent diseases such as secondary pyoderma, inadequate dosing (only once daily treatment, even dogs on liquid formulation may need twice daily administration), therapy not long enough, poor owner compliance, poor bioavailability, un-registered product/internet pharmacy, inactive thyroxine, poor gastrointestinal resorption.
Thyrotoxic effects of excessive T4 supplementation occur only rarely in dogs and among others include polydipsia, polyuria, polyphagia, panting, weight loss, or hyperactivity.

Prognosis of hypothyroid dogs if treated and monitored adequately, is excellent.

References:
Available from author upon request.